RESEARCH ETHICS

Partnership as an ethical model for medical research in developing countries: the example of the ''implementation trial''

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The existing model for ethical review of medical research consists primarily of regulations designed to prevent exploitation of participants. This model may fail when reviewing other ethical obligations, particularly the responsibility to provide valuable knowledge to society. Such failure is most apparent in developing countries, in which many stakeholders lack incentives or power to uphold society's interests. An alternative ethical model is that of partnership, which actively involves all partners during ethical review and aims to secure partners' best interests through compromise. Unlike the existing ''regulatory'' model, the partnership model effectively addresses ethical obligations to provide positive benefits to society. For the partnership model to be effective, power must be shared among partners; thus, the partnership model can be harmonised with the ''regulatory'' model through explicit consideration of power structures. One opportunity for crafting power balance in developing countries is apparent in ''implementation trials''—randomised trials motivated by and integrated into the implementation of long term public health interventions. Given the failings of the existing ethical review model, alternative models—for example, partnership—and means to balance power—for example, implementation trials—must be explored to ensure that medical research provides knowledge of value to societies in the developing world.

A central theme in medical research ethics is the prevention of exploitation. Indeed, many of the documents that have guided research ethics for the past 40 years[1–3] were developed in response to specific incidents of exploitation of research participants.[4] Under the ethical framework set forth in these documents, medical research is evaluated according to certain ethical guidelines—namely respect for autonomy, beneficence and non-maleficence, and justice. The goal of this ethical framework is ostensibly ''to protect the subjects of biomedical research from abuse and exploitation''.[5]

This preoccupation with preventing exploitation has led to a ''regulatory'' model of ethical review. Under this model, ethical review boards have interpreted the above guidelines as a series of minimum ethical standards—including adequate informed consent, favourable risk/benefit ratios, and representative patient populations[6]—that are used to determine whether research is ethically acceptable. In the event of non-compliance with these standards, protocols can be rejected or sanctions—from refusal to publish results to suspension of eligibility to receive research funding—can be imposed.[3] The focus on regulation, standards, and compliance reflects a desire to ensure a minimum threshold of ethical acceptability—namely that research participants are not exploited.

This ''regulatory'' ethical model, when applied conscientiously, has greatly enhanced protections for research participants against exploitation,[7] but it fails to address other key ethical obligations of medical research, most notably the generation of ''generalisable knowledge to improve health and/or increase understanding of human biology''.[8 9] Medical research must provide valuable knowledge to society. Whereas the regulatory model prevents ethical *harm* to *participants* (''negative'' ethical obligations), this obligation involves ethical *benefit* to *society* (a ''positive'' obligation). The failure of the regulatory model to address such positive ethical obligations to society is reflected in pleas to consider ''relative value'' rather than minimum standards when reviewing the scientific and social value of research.[8 10]

Since the ''regulatory'' model of ethical review fails to ensure that medical research provides valuable knowledge, this responsibility falls in fact to groups that do not evaluate this function as an ethical obligation to society. These groups include investigators who design and conduct studies, agencies that perform scientific review, ethical review boards that consider risk/benefit ratio to individual participants, and government bodies providing legal regulation. The potential for ethical breach is greatest when these groups lack incentives, capacity, or power to uphold society's interest in obtaining valuable knowledge.

While investigators, scientific or ethical review boards, and regulators are not ideal guardians of society's interests in the developed world, their capacity to speak for society in developing countries is particularly weak. In developing country medical research, investigators and funders often hail from developed countries,[11] local institutional review boards often lack sufficient expertise or power to reject protocols approved by their developed country counterparts,[12 13] and regulatory bodies often have strong financial and political incentives to approve research proposals.[14] As a result, the ethical obligation of medical research to provide valuable knowledge to developing societies often goes unfulfilled. Forty per cent of United States researchers agreed, for example, that ''research priorities of their funding agencies were incongruent with the top priorities of the developing country in which they were conducting research'',[15] and even basic findings are often not communicated to key stakeholders, including coordinators of health research and policy agendas, in the developing countries where studies are conducted.[14]

Abbreviations: GHIS, Gambia Hepatitis Intervention Study; HBV, hepatitis B vaccine

This routine violation of a basic ethical obligation may be addressed by expanding the ethical review process to address obligations other than the protection of research participants. Given the critical importance of preventing exploitation and the success of the ''regulatory'' model in this respect, however, a method is also needed to harmonise any expanded approach with the existing ethical framework. One potential model for addressing positive ethical obligations to society is that of partnership,[11 16] and one method of harmonising the partnership and ''regulatory'' models is the explicit review of power structures.

A PARTNERSHIP MODEL FOR ETHICAL REVIEW

The characteristics of research partnerships between developed and developing countries include such activities as mutually developing research objectives; building trust; sharing information, responsibility, and profits; and creating transparency.[11 17] The essential parties in such research partnerships include, at a minimum, researchers, government organisations, community leaders, and potential participants.[16] Importantly, partnership provides a mechanism for crafting a new model of ethical research review that addresses the aforementioned failings of the ''regulatory'' model.

By focusing on societal stakeholders as partners rather than on investigators and research participants as potential exploiters and victims, a partnership model for ethical review would differ from the existing ''regulatory'' model in at least two ways. First, the review process would more actively involve all partners. Under the ''regulatory'' model, ethical review boards often meet in private, working directly with investigators to modify research protocols, but failing to provide a direct voice to other stakeholders in each given research proposal, including policy makers, community representatives, and potential research participants.[18 19] A model of ethical review that views these stakeholders as partners would encourage open and active discussions between all parties, rather than fostering a regulatory relationship between review boards and investigators alone. Second, under a partnership model, the goal of the ethical review process would shift from the fulfilment of minimum ethical standards and protections to the achievement of partners' best interests through compromise. Ethical review boards would participate in these discussions as arbitrators and advocates for the interests of vulnerable or disenfranchised partners rather than as regulators.[18 20] Regulations to protect research participants from exploitation could remain in place, but would be fulfilled by an agreement or contract between partners, rather than a stamp of ethical approval from the review board. The scope of this agreement would extend beyond the fulfilment of minimum ethical standards to addressing the best interests of all parties.

If implemented, a partnership model of ethical review would overcome many of the shortcomings of the existing ''regulatory'' model. By actively engaging partners (including policy makers and community leaders) who are better positioned to speak for society's interests, this model better addresses ethical obligations of researchers to society. By shifting the goals of the review process to the achievement of best interests rather than avoidance of ethical transgression, the partnership model implicitly incorporates positive ethical obligations. Finally, the partnership model need not abrogate existing protections under the regulatory model; ethical review boards may refuse to sign any agreement failing to meet existing ethical standards, and assent of the board (as a partner in the review process) could be required for the agreement to take effect. Thus, a partnership model of ethical review may address many of the existing regulatory model's failings without necessarily sacrificing its protections.

BRIDGING THE MODELS: POWER STRUCTURES

While a partnership model of ethical review has certain advantages, particularly in developing countries where the failings of the regulatory model are greatest, it is clear that not all research arrangements function as partnerships.[16] Therefore, a method is needed to judge whether the partnership model is appropriate for evaluating specific research proposals. One such method is the explicit assessment of power structures during the process of ethical review. There exists ''an intimate link between ethics and power'', in that power imbalances—shaped by differences in financial and knowledge resources, social and political authority, or ability to reward and punish—facilitate exploitation.[21 22] To the extent that power is equalised between two parties, the ability of one to exploit the other is diminished. Currently, most review boards employ ''regulatory'' ethical guidelines without explicitly considering the power structures between various stakeholders.[5] Furthermore, by failing to give research participants a more active voice during ethical review, these boards unintentionally reinforce participants' lack of power in the research process.[18]

Explicit consideration of power structures would enable review boards to assess the potential for exploitation of research participants and thus the need to employ the regulatory model in order to protect those subjects. In cases where more balanced power structures are convincingly demonstrated, review under the partnership model might be more appropriate. Incentives—for example, a more streamlined and collaborative review process—could encourage both the formation of power balanced research collaborations and their review under a partnership model. Consideration of power structures during ethical review might also correct a further weakness of the current review process, namely its common failure to provide sufficient additional protections to ''vulnerable'' populations—for example, women in many developing countries.[20] By explicitly recognising such instances of extreme power imbalance, ethical review boards would empower themselves and researchers to provide any additional safeguards necessary.

Thus, it is proposed that the existing ''regulatory'' model for ethical review of research protocols be expanded to include an explicit assessment of the power structures underlying each proposal. When power is judged to be reasonably balanced between investigators, policy makers, community members, and research participants, superior ethical review may be achieved through adoption of a partnership model that actively involves these stakeholders and seeks to craft an agreement achieving each party's best interests. This process is particularly relevant for research carried out in developing countries, where the existing model is weakest and power imbalances often most severe. Essential to implementing a partnership based process of ethical review is the identification of opportunities for effectively sharing power in developing country research.

IMPLEMENTATION TRIALS AS EXAMPLES OF RESEARCH PARTNERSHIPS

The randomised trial, a study design in which participants from a defined population are randomised to different treatment arms and evaluated for specific outcomes, is widely considered the ideal design for evaluating the efficacy of new interventions.[23] The ethical acceptability of conducting randomised trials in developing countries under the current ''regulatory'' model remains, however, the subject of fierce debate.[24] Thus, randomised trials in developing countries stand to benefit greatly from ethical review under the partnership model, which in turn requires that partners be sufficiently empowered to engage in open discussion and speak for their own best interests.

One opportunity for balancing power in developing country randomised trials is the ''implementation trial'', defined here as a randomised trial that is motivated by and integrated into the implementation of a long term public health intervention. Ideally, the execution of this intervention is planned to occur even in the absence of the implementation trial, and although the trial has a defined end—for example, when study outcomes are no longer evaluated—the intervention is intended to continue after trial completion. In contrast to standard randomised trials that plan to provide interventions (if found to be efficacious) to all participants at study completion,[3] implementation trials specifically plan to distribute the intervention beyond the study population. Furthermore, implementation trials differ from trials that provide ancillary assistance—for example, medical care—to the surrounding community, in that implementation trials evaluate and are motivated by the accompanying interventions. As an example of an implementation trial, the Gambia Hepatitis Intervention Study (GHIS) randomised communities with over 100,000 infants to begin receiving hepatitis B (HBV) vaccine at different times over a four year period, as part of a new national policy of universal HBV vaccination.[25]

Implementation trials offer unique opportunities for balancing power in study development, design, and execution between researchers from the developed world and other stakeholders, including policy makers, community members, and research participants. Certainly, not all implementation trials necessarily incorporate such balance of power, nor is power balance unachievable in the context of other trials. Rather, implementation trials are described here to illustrate the features of trials that share power and which, therefore, may be amenable to ethical evaluation under the partnership model.

Regarding study development, the primary research question in an implementation trial often reflects the interests of researchers, policy makers, the surrounding community, and potential participants—for example, the GHIS was designed with two primary research aims, namely (1) to evaluate the efficacy of HBV vaccination against infection and later disease, and (2) to demonstrate the feasibility and effectiveness of including HBV as a routine immunisation in an African country.[26] Both of these aims addressed researchers' desire to produce knowledge that could be used generally but were also directly relevant to Gambian policy makers and citizens whose children would be compulsorily vaccinated. Furthermore, the trial could be justified ethically and financially based solely on its benefit to The Gambia. Thus, Gambian partners had greater power in directing the trial's goals, acting as approximate equals with researchers in developing the trial's primary aims.

Regarding study design, implementation trials often reflect the strategy for scaling up the accompanying public health intervention, over which partners from developing countries have ultimate control. The resulting increase in power of developing country partners may profoundly affect the statistical methodology employed. From the perspective of researchers—for example—it is undesirable and even unethical to incorporate statistical inefficiencies such as an unnecessarily large sample size.[27] Other partners may, however, perceive greater ethical good in statistical methods that address their need to gradually and comprehensively scale up public health interventions. When power balance between partners is achieved, the agreed upon statistical methodology may incorporate concessions from researchers in order to serve the best interests of other partners. For example, GHIS employed a cluster randomised design with a ''stepped wedge'' randomisation scheme. Under this design, one new cluster is randomised to receive the intervention per unit time, with the comparison group consisting of clusters not yet providing the intervention.[25] By study end, all clusters receive the intervention.

Compared to an individually randomised design, cluster randomised trials require larger sample sizes and more complex analysis because of potential correlations between participants in the same cluster.[28] Furthermore, the stepped wedge design requires additional increases in sample size and introduces potential bias from time effects.[29] Some researchers argue that stepped wedge trials and traditional trials are ethically equivalent because both designs ultimately provide any effective intervention to all participants and require equal amounts of person time in the non-intervention arm; indeed, if intervention efficacy is rapidly demonstrated, the stepped wedge design may delay the distribution of that intervention to the study population (Lawrence Moulton, personal communication, 2005). In the case of GHIS, however, the stepped wedge design allowed other partners to adapt to the logistics of gradually scaling up a public health intervention and relieved some of the ethical tension surrounding maintenance of a placebo arm. Thus, power sharing between partners may dramatically affect statistical methodologies and other features of study design. Implementation trials may provide a forum for testing novel design features aimed at maximising ethical benefits derived by all partners.

Regarding study execution, implementation trials often require shared responsibility—and thus shared power—over conduct of trial activities. Whereas researchers from developed countries generally design and execute traditional randomised trials, implementation trials are motivated by and integrated into larger interventions that must be implemented by non-research personnel once the trial is completed. As such, other partners must take an active role in trial execution. Once GHIS finished its four year timeline, for example, the Gambian government assumed responsibility for universal HBV vaccination of Gambian infants, a policy facilitated by the experience and scientific results from GHIS.[30] Thus, implementation trials provide opportunities for balancing power between partners in study execution, as well as in development and design. To the extent that power imbalances can be diminished in implementation trials or other studies, the partnership model may become a more appropriate perspective for ethical review of medical research.

LIMITATIONS OF THE PARTNERSHIP MODEL

The partnership model, while potentially valuable as an addition to the ethical review process, is not universally applicable. Specifically, the partnership model will not correct power imbalances: stakeholders—for example, research participants and community members—who lack power will require ''regulatory'' protections, not naïve treatment as partners. Rather, the partnership model is proposed as a mechanism for achieving greater ethical benefit once relative power balance is achieved. Implementation trials represent one limited example of an opportunity to improve such balance, but are appropriate only for studies of interventions whose wide scale implementation is already planned. Since many studies of great importance to the developing world will not meet this criterion, it is essential to identify additional opportunities for balancing power in developing country trials. Further limitations of the partnership model include difficulty in selecting appropriate representatives from each partnering group—for example, the community[19]—and the need for a continuing mechanism to protect research participants and other partners when power balance breaks down.

CONCLUSION

In summary, the existing ''regulatory'' model of ethical review, developed in response to specific instances of

exploitation toward research participants, fails to address two types of fundamental ethical obligations, namely those to parties other than research participants and those that demand positive benefits. These failings are most severe in developing countries, where safeguards for such obligations are weakest. A partnership model, which encourages active involvement of all partners with a goal of achieving best interests through compromise, may better address such ethical obligations. The partnership model cannot be effectively employed, however, unless power is first shared among partners; thus, explicit evaluation of power structures is also essential. Implementation trials, in which randomised trials are motivated by and integrated into the implementation of long term public health interventions, present one opportunity for crafting power balance in developing country randomised trials. Given the failings of the existing ''regulatory'' model for ethical review, alternative models—for example, partnership—and means to balance power—for example, implementation trials—must be explored and tested so that medical research can meet its continuing ethical obligation to provide knowledge of value to societies in the developing world.

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